REMARKS

In order to simplify the issues under consideration in this case, claim 60 and all claims dependent thereon, have been canceled. In addition, claim 24 and all claims dependent thereon have been amended to delete the recitation of antibody fragments. No new issues requiring further consideration or search are raised by the proposed claim amendments, and since the amendments reduce the number of claims and reduce the issues for possible appeal, their entry is respectfully requested. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier. Applicant respectfully requests further consideration of the present application in light of the following remarks.

Independent claim 24 is directed to a treatment method that uses an immunoconjugate that comprises (i) at least one human, humanized or chimeric anti-CD22 antibody, and (ii) a drug or a radioisotope, wherein said radioisotope is other than ^{131}I, wherein the immunoconjugate is used in combination with a naked anti-CD20 mAb. None of the cited references disclose or teach the combination of anti-CD22 immunoconjugate and naked anti-CD20 antibody as described in claim 24 and claims dependent thereon.

Claims 60-70, 73-79 and 91-93 are rejected under 35 U.S.C. §102(e) based on United States Patent No. 5,789,554 and claims 60-70, 73-77, 79 and 91-93 are rejected under 35 U.S.C. §102 (b) based on WO 96/04925. Claims 60-65, 67-69 and 91-95 are rejected under 35 U.S.C. §102(b) based on Juweid *et al.*, and claims 60-89 and 91-97 are rejected under 35 U.S.C. §103(a) based on Juweid *et al.* in view of United States Patent No. 5,698,178. All of these rejections are obviated by the cancellation of claims 60-97.

Claims 24-26, 36-38, 44, 45, 47, 52, 55-57, 60-70, 73-79 and 91-93 are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and Li *et al.* Claims 24-27, 36-38, 44, 45, 52, 55-57, 60-70, 73-79 and 91-93 are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and United States Patent No. 5,106,955. Claims 24-26, 36-42, 44, 45, 52, 55-57, 60-70, 73-77 and 91-93 are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and United States Patent No. 5,686,072 and PCT publication WO 95/09917. Claims 24-26, 36-39, 44, 45, 52, 55-57, 60-70, 73-77 and 91-93 are rejected under 35 U.S.C. §103(a) based on United

States Patent No. 5,789,554 in view of Maloney *et al.* and European Patent Application No. 510949. Claims 24-27, 36-38, 43-45, 52, and 55-89 and 91-97 are rejected under 35 U.S.C. §103(a) based on United States Patent No. 5,789,554 in view of Maloney *et al.* and United States Patent No. 5,698,178. Claims 24-27, 38, 43-45, 52, 55-89 and 91-97 are rejected under 35 U.S.C. §103(a) based on WO 96/04925 in view of Maloney *et al.* and United States Patent No. 5,698,178.

All of these rejections are based on the combination of United States Patent No. 5,789,554 ("Leung") in view of Maloney *et al.* ("Maloney") with the addition of one or two additional references, and Maloney is the sole reference cited in support of the obviousness of combinations of anti-CD22 immunoconjugates and anti-CD20 naked antibodies. Therefore, once the impropriety of this portion of the rejection is established, all of the rejections based on Leung and Maloney must fall.

Leung describes immunoconjugates of LL2 with cytotoxic agents or labels (see abstract). The examiner admits that Leung does not teach combinations of LL2 with anti-CD20 antibodies as recited in claim 24 and claims dependent thereon, but urges that it would have been obvious to combine anti-CD22 immunoconjugates and naked anti-CD20 antibodies base on the disclosure in Maloney of treating B-cell lymphoma, NHL, and other leukemias and lymphomas with a chimeric anti-CD20 monoclonal antibody, rituximab. She argues that a skilled artisan would have expected a mixture of antibodies to the different epitopes "would be more efficacious in therapeutic methods, as well as enhance the treatment modality," citing the last paragraph on page 2465 of Maloney.

The cited portion of Maloney discloses that "extension of these studies to patients with minimal disease, using antibody alone or in combination with ***conventional therapies***, may provide the greatest benefit. "Conventional therapies" at the time of the Maloney article, circa 1994, were chemotherapies, not antibody therapies. Therefore, the disclosure in Maloney that anti-CD20 may be combined with a "conventional therapy" would not have suggested a combination with anti-CD22 immunoconjugate therapy, as presently claimed. No *prima facie* case of obviousness exists.

Moveover, Maloney *teaches away* from any use of immunoconjugates, and thus is improperly combined with Leung to allege the obviousness of the presently recited combination. "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, ***would be discouraged*** from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Gurley*, 31 U.S.P.Q.2d 1130 (Fed. Cir. 1994), emphasis added. More recently, in *Ecolochem, Inc. v. Southern California Edison*

Company, 227 F.3d 1361 (Fed.Cir. 2000), cert. den., 121 S.Ct. 1607, the Federal Circuit noted that the combination of two prior art references does not render patent claims obvious if there was no evidence of any suggestion, teaching, or motivation to combine the information from the prior art and where there was evidence that the prior art actually taught away from the patented process. In *Ecolochem*, the prior art taught away from a mixed-bed ion exchange process; therefore, no motivation existed for one of ordinary skill in the art to produce the patented technology.

Similarly, here Maloney teaches away from the use of antibodies that are radiolabelled or conjugated to a cytotoxic agent, noting that:

> The [anti-CD20] antibody preparation is used directly for therapy, not requiring conjugation to drugs, toxins, or radiolabels, each of which requires extensive safety testing and may not be stable after formation of the active conjugate. Antibody modification may interfere with antigen binding... significant hematologic toxicity is associated with the use of high-dose radiolabeled conjugates...In some studies, immunotoxin conjugates have been associated with significant toxicities (page 2585, penultimate paragraph).

Thus, a skilled artisan ***would be discouraged*** from the very combination urged to have been obvious by the examiner. The combination of Leung and Maloney would not have suggested therapy with a combination of an anti-CD22 immunoconjugate and a naked anti-CD20 antibody. No *prima facie* case of obviousness of claim 24 and claims dependent thereon is supportable based upon the combination of a primary reference that teaches the use of immunoconjugates (Leung) and a secondary reference (Maloney) that teaches the use of naked antibodies and specifically teaches away from any use of immunoconjugates.

Claims 24-27, 36-45, 47, 52, 55-89 and 91-97 are provisionally rejected under the doctrine of obviousness-type double patenting over claims 24-44 of co-pending application No. 10/3 14,330. The examiner states that applicant's request has been considered but found unpersuasive and the rejection is maintained. Applicant did not request that the rejection be withdrawn, but merely that it be held in abeyance until such time as allowable subject matter is indicated in one of the two applications. Until such time, the rejection is "provisional" and is indicated as such in the Official Action. According to MPEP 822.01:

> The "provisional" double patenting rejection should continue to be made by the examiner in each application as long as there are

> conflicting claims in more than one application unless that "provisional" double patenting rejection is the only rejection remaining in one of the applications. If the "provisional" double patenting rejection in one application is the only rejection remaining in that application, the examiner should then withdraw that rejection and permit the application to issue as a patent, thereby converting the "provisional" double patenting rejection in the other application(s) into a double patenting rejection at the time the one application issues as a patent.

Thus, no further action on applicant's part with respect to the provisional double patenting rejection is required. Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

If there are any problems with this response, Applicant's attorney would appreciate a telephone call. In view of the foregoing, it is believed none of the references, taken singly or in combination, disclose the claimed invention. Accordingly, this application is believed to be in condition for allowance, the notice of which is respectfully requested.

Respectfully submitted,

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